

## Canine leishmaniasis – a new danger for British dogs. How to recognize and treat it.

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Leishmaniasis is a canine cutaneous and visceral disease caused by the protozoal agent *Leishmania donovani*. This is a dimorphic parasite, which requires two different hosts, a vertebrate and an insect, to complete its cycle. *Leishmania* is vectored by nocturnal sandflies of the genus *Phlebotomus spp.*, which are found in the Mediterranean area, Africa, Middle East, India and China. The absence of this specific insect vector in the United Kingdom makes the transmission between dogs, and from dog to man, impossible.

Prevalence of seropositivity for leishmaniasis among dogs living in endemic area is very high (up to 50%). Seropositive dogs have had a contact with the parasite, but not all of these will develop the clinical disease. In fact about 20-40% of them will never show signs of the disease and will turn seronegative in a few weeks to months. The others, sooner or later, will develop the disease. The incubation period may be very long, so that dogs travelling abroad can show signs of the disease once returned to the UK, even several years thereafter, making it a diagnostic challenge for the British veterinarian.

It is the immunologic status of the individual dog that determines if the animal will develop or not the clinical disease. Some dogs with a strong cell-mediated immune system (so called Th-1 type) are able to get rid of the parasite, other dogs with a weaker cell-mediated response will allow its colonization and multiplication in the macrophages and dissemination to bone marrow, lymphnodes, spleen and liver. These latter group of dogs usually develops an important humoral antibody response (so called Th-2 type), which is useless for the elimination parasites and causes high amounts of damage to the body organs.

Clinical signs of infection are various and involve many organs. Most often the skin is affected with an exfoliative dermatitis, sometimes associated with alopecia, starting from the head and slowly involving the rest of the body. Other cutaneous signs are small crusts and ulcers (caused by vasculitis) on mucocutaneous junctions, extremities and pressure points (bony prominences). On occasion nasal depigmentation, ulceration and epistaxis may be observed. Blepharitis is often seen. Occasionally small nodules may be seen, particularly on glabrous areas, which most probably represent reactions at inoculation sites. Rarely nodules can be observed on mucous membranes, such as in the mouth or on the penis. Leishmaniasis is usually a non-pruritic condition.

Other non-cutaneous signs are often associated with the cutaneous disease. The most frequent ones are generalized lymphadenopathy, weight loss in spite of an excellent appetite, weakness and decreased physical activity, and an "old" aspect in spite of a young age. The high amounts of antibodies produced form circulating immune-complexes, which deposit in filtering membranes, causing vasculitis (as already mentioned above), uveitis, arthritis with shifting leg lameness, and glomerulonephritis. Renal insufficiency is ultimately the most frequent cause of death in untreated dogs affected by leishmaniasis. Less frequent signs of leishmaniasis are diarrhea, hemorrhagic enteritis, pancreatitis, chronic active hepatitis, vomit, heart disease and thrombosis.

Differential diagnoses of the clinical exfoliative form are sebaceous adenitis and other keratinization disorders. Some alopecic forms may mimic endocrine diseases. Vasculitis can be caused by several other causes, including septicaemia, other blood parasites or autoimmune diseases. The nasal depigmentation and ulceration is observed also in cutaneous lupus and in epitheliotropic lymphoma. The latter one also can present with an exfoliative form similar to that of leishmaniasis, however it is usually very pruritic. The nodular form may mimic other multicentric nodular diseases, such as multiple histiocytomas (especially in boxers and shar-peis), cutaneous histiocytosis and others multicentric tumours.

The systemic signs may be similar to other infections, particularly ehrlichiosis, to which leishmaniasis is often associated. Generalised lymphadenopathy is also observed in malignant lymphoma. Symptoms caused by the deposit of immune complexes (polyarthritis, glomerulonephritis, vasculitis and skin ulcers) are also observed in systemic lupus erythematosus (SLE), its major differential diagnosis. ANA titres can be positive in leishmaniasis, making the differentiation between the two diseases very difficult. If a dog has been in an endemic area and shows signs compatible with SLE, it is very important to exclude leishmaniasis before initiating an immune suppressive therapy.

In any dog with compatible clinical signs, which has been in an endemic area in spring, summer or autumn, a leishmaniasis should be seriously considered. It would be ideal, for a definitive diagnosis, to visualize the parasite in cytologic smears of lymph nodes or of bone marrow, however this is not always possible (positive in 30-70% of the cases). Cytologic preparations can also be obtained with impression smears from beneath crusts and scales or by fine needle aspiration biopsies from skin nodules. Parasites may also be observed in histologic sections of skin or lymph node biopsies, particularly if immunohistochemical techniques are used.

Serological tests for the measurement of leishmania-specific antibodies have a high sensitivity and specificity, but can give false positive results in resistant animals which have just got in contact with the parasite, or false negative results in animals in the prepatent phase. Serological tests are not suitable as a means of monitoring treatment efficacy, as antibody titre may remain measurable even after clinical remission. Together with a leishmania specific serum test, total serum protein should be measured and a protein electrophoresis should be performed. A leishmania titre above 1/80, high serum proteins (above 8 g/l), low albumines and high globulines are highly suggestive of leishmaniasis. If the titre is positive, but the serum protein and electrophoresis are normal, it is advised to repeat the tests after 1 month.

Before starting the treatment it is important to assess the renal status, by measuring blood urea and creatinine, cholesterol, and with a complete urine analysis. A compromised renal function may require specific therapy and negatively affect the prognosis.

Several molecules and treatment protocols have been suggested, but none of these is capable of completely eliminating the parasite from the host, and relapses of the disease are very common. A recent systematic analysis of the published literature on the topic has reported that the best treatment option is represented by meglumine antimoniate associated with alopurinol. Meglumine antimoniate is administered subcutaneously at the dosage of 100 mg/kg per day for one month, together with the oral administration of 15.25 mg/kg twice daily alopurinol per os. After one month, if the clinical signs have greatly improved and the serum protein electrophoresis has returned to normal values, glucantime meglumine injections can be stopped, while it is important to continue the alopurinol administration. In case of no improvement, then a second month of therapy is advised, together with testing for other agents, such as Ehrlichia and Rickettsia. Once the dog is in good clinical condition and presents a normal electrophoretic profile, a maintenance regimen can be started, based on oral alopurinol administration as described above, for a minimum of one year, or even better for the rest of its life. Control serum protein electrophoresis should be performed each month for the first 6 months and twice yearly thereafter. In case of relapse, therapy with glucantime meglumine and monitoring of protein electrophoresis should be started again as described above. If treated with this protocol affected dogs have a 75% chance of surviving at least four years.

Alternative therapies are less recommended. They include the use of allopurinol alone, amphotericin B, enrofloxacin, metronidazole/spiramicyn and metronidazole with enrofloxacin.

The best means of prevention for dogs usually living in the UK is not to travel in endemic areas. If this is not possible, then dogs should be protected with repellent products against sandflies before and during the trip. A deltamethrin collar has been proven to be effective in decreasing by 50% the infection rate. A similar protection is offered by microencapsulated permethrin sprays or spot ons. It is advised not to allow the dog outside between sunset and sunrise, and to apply fine mesh nets to the windows. Asymptomatic dogs should not be tested before 3 months from their return from an endemic area.